The Usage of Oral Anti Hyperglycemic Agent in Gestational Diabetes: Pros and Cons

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Abstract

The prevalence of gestational diabetes mellitus (GDM) is increasing as the pregnant population becomes older and more obese. Fifteen percent of GDM patients require medical intervention. Insulin is still the drug of choice because it has not been implicated as a teratogen in human pregnancies. Insulin has its disadvantages such as the need for injections, the risk of hypoglycaemia, excessive weight gain and the costs. The use of oral anti hyperglicemic agent (OAHA), traditionally contraindicated, now can be considered as an alternative for insulin which can be beneficial in developing countries. From four groups of OAHA, sulfonylurea and biguanides can be used during pregnancy. Studies and randomized controlled trial (RCT) have been done and most summarized that it does not increase any maternal and perinatal morbidity. Most data also show that there are also no differences in glycemic control or pregnancy outcomes compared with insulin. There are conflicting data shows metformin increase prevalence of preeclampsia patient and perinatal morbidity. OAHA usage, although not yet recommended internationally, can be considered in GDM patients with uncontrolled blood sugar levels that require medical intervention but can not use insulin. Well conducted, prospective, controlled studies regarding its feasibility in pregnant women with diabetes are still needed.

***Keywords**: oral antihyperglycemic agent, gestational, diabetes*

Penggunaan Obat Hipoglikemik Oral pada Diabetes Gestasional: Pro dan Kontra

Abstrak

Prevalensi diabetes mellitus gestasional (DMG) meningkat karena ibu hamil semakin lama semakin tua dan gemuk. Sebanyak 15% pasien DMG memerlukan intervensi medis. Insulin merupakan obat pilihan karena tidak teratogen pada kehamilan, namun memiliki kelemahan yaitu memerlukan suntikan, risiko hipoglikemia, berat badan berlebihan dan biaya. Obat hipoglikemik oral (OHO) dapat digunakan sebagai pengganti insulin terutama di negara berkembang. Dari empat kelompok OHO, sulfonilurea dan biguanid dapat digunakan selama kehamilan. Studi dan randomized controlled trial (RCT) menyatakan bahwa OHO tidak meningkatkan morbiditas ibu dan bayi. Sebagian besar data juga menunjukkan tidak ada perbedaan dalam kontrol gula atau luaran kehamilan dibandingkan dengan insulin. Meskipun demikian terdapat data yang menunjukkan peningkatan prevalensi preeklampsia dan morbiditas perinatal pada penggunaan metformin. Penggunaan OHO, meskipun belum direkomendasikan secara internasional, dapat dipertimbangkan pada pasien DMG dengan kadar gula darah tidak terkontrol yang memerlukan intervensi medis tetapi tidak dapat menggunakan insulin. Perlu dilakukan studi prospektif dan terkontrol mengenai kelayakan pengunaannya pada ibu hamil dengan diabetes.

***Kata Kunci**: obat hipoglikemik oral, gestasional, diabetes*

Introduction

Gestational diabetes mellitus (GDM) is associated with a higher rate of adverse pregnancy outcomes and various neonatal complication.[1-3] Its prevalence in the United States is 3–5%, which accounts for 90–95% of diabetes mellitus (DM) occurring in pregnancy. [2] The prevalence is increasing as the pregnant population becomes older and more obese. The cornerstone of treating a GDM patients is a well-adjusted diet, combined with patient education and adapted physical exercise routines.[4] Approximately 15% of GDM patients will not meet glycemic targets with diet alone and will require medical intervention. insulin is still the drug of choice because it has not been implicated as a teratogen in human pregnancies.[1, 4-6] Insulin, as the drug of choice, has its disadvantages such as the need for injections, the risk of hypoglycaemia, excessive weight gain and the costs involved.[5] The use of OAHA that was traditionally contraindicated during pregnancy can now be considered as an alternative for insulin therapy which can be beneficial in developing countries where the proper use of insulin is problematic.[4-5]

Gestational Diabetes Mellitus

GDM is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy.[2-3,6] The overall incidence has steadily increased over time, ranging from 2.2% in South America to 15% in India. Infants whose mothers have DM are at an increased risk for future insulin resistance. This association, along with the recently increased prevalence of obesity and type 2 DM, may lead to a significant rise in the occurrence of GDM, with a consequent cycling of obesity, insulin resistance, DM, and various metabolic complications in future offsprings. There is a higher rate of hypertensive complications in diabetic pregnancies compared with normal pregnancies.[7-8] In addition, pre-pregnancy obesity and DM also increase the risk of cesarean section delivery. Infants born to women with GDM are at an increased risk of stillbirth, aberrant fetal growth, birth trauma, and various metabolic and electrolyte disturbances. Congenital malformations, perinatal mortality, macrosomia, neonatal hypoglycemia, neonatal hypocalcemia, neonatal polycythemia and neonatal respiratory distress is more frequently encountered in infants of mothers with DM compared with those of non-diabetic mothers.[1, 6]

GDM is detected by the screening of pregnant women,[1,3,6] followed, as necessary, by diagnostic measures. Two approaches may be followed for GDM screening at 24 to 28 weeks: a two-step approach that was performed initially by measuring plasma or serum glucose 1 hour after a 50 gm oral glucose load and perform a diagnostic 100 gm OGTT on a separate day in women who exceed the chosen threshold on 50 gm screening. The other step is one-step approach that perform a diagnostic 100 gm OGTT in all women to be tested at 24 to 28 weeks. The 100 gm OGTT should be performed in the morning after an overnight fast of at least 8 hours. The one step approach can be used in place with high prevalence of GDM. Some cut off values of the OGTT 100 and 75 gram can be seen in Table 1.

Table 1. Cut-off Values for the OGTT 100 and 75 gm[1]

Study	Fasting	1 hour	2 hours	3 hours
100 gram Carpenter and Coustan	95 mg/dl (5.3 mmol/l)	180 mg/dl (10.0 mmol/l)	155 mg/dl (8.6 mmol/l)	140 mg/dl (7.8 mmol/l)
100 gram National DM Group	105 mg/dl (5.8 mmol/l)	190 mg/dl (10.6 mmol/l)	165 mg/dl (9.2 mmol/l)	145 mg/dl (8.0 mmol/l)
75 gram WHO	126 mg/dl (7.0 mmol/l)	-	140 mg/dl (7.8 mmol/l)	-
75 gram American Diabetes Association	95 mg/dl (5.3 mmol/l)	180 mg/dl (10.0 mmol/l)	155 mg/dl (8.6 mmol/l)	-
75 gram Canadian Diabetes Association	95 mg/dl (5.3 mmol/l)	190 mg/dl (10.6 mmol/l)	160 mg/dl (8.9 mmol/l)	-

Gestational Diabetes Mellitus Management

The single most important step to achieve minimal morbidity and mortality rates in GDM is to establish near-normal metabolic control.[1] Diet and behavioral adjustments are needed. Total daily caloric intake that should be allowed per day is calculated according to current and ideal body weight. Caloric distribution must also be accounted because insulin resistance is highest in the morning as a result of physiological secretion of cortisol. Therefore, carbohydrate-based calories should be consumed at later times of the day, and breakfast should only be a small meal. Also, exercise addresses the issue of insulin resistance, thus may be a useful add-on therapy.[1-3, 6] If nutritional therapy fails to attain the targets (which comprise < 95 mg% FPG and preprandial glucose and < 120 mg% postprandial glucose), insulin therapy is instituted. Approximately 15% of GDM patients will not meet glycemic targets with diet alone and will require medical intervention.[1-2] Regular human insulin is most frequently prescribed; however, either human regular insulin or rapid-acting analogues can be used by means of multiple daily injections or subcutaneous infusion.

There are several protocols for insulin distribution throughout the day via several timed daily injections and according to glycemic control.[1-2,5,9] One common regimen involves giving two-thirds of the total calculated daily insulin dose in the morning (fasting, pre-breakfast), made up of two parts intermediate-acting to one part regular insulin. The remaining one-third of the total daily dosage should be divided equally as regular insulin (to be given before dinner) and intermediate-acting insulin (at bedtime). However, Insulin, as the drug of choice, has its disadvantages such as the need for injections, the risk of hypoglycaemia, excessive weight gain and the costs involved.

Oral Antihyperglycemic Agent:
A new options in Gestational DM treatment

OAHA have traditionally been avoided in women with DM in pregnancy because of the potential risks of neonatal hypoglycemia, congenital anomalies, neonatal hyperbilirubinemia and teratogenicity associated with placental transfer to the fetus.[10]

It have been implicated that first generation sulfonylureas are teratogens in animal studies although these early studies failed to show conclusively that the compounds themselves and not altered maternal metabolism, were the primary teratogen. OAHAs are divided into four groups: derivatives of sulfonylurea, biguanides, glucosidase inhibitors and thiazolidinediones.[7, 9]

Sulfonylureas cause hypoglycemia by stimulating insulin release from pancreatic beta cells.[9] Their effects are initiated by binding to, and blocking, an adenosine triphosphate (ATP)-sensitive potassium channel. First-generation sulfonylureas have been shown to cross the placenta. However, there is conflicting evidence regarding the newer second generation drugs.[5] With regards to the second-generation sulfonylurea agents glibenclamide and glipizide, no teratogenic effects were observed in rats and rabbits administered large doses of these agents.[4] A major concern with the use of OAHAs during pregnancy is neonatal hypoglycemia which may be severe and persist for days. Early studies in rats and mice have suggested that tolbutamide and chlorpropamide are teratogenic. However, they failed to show conclusively that these drugs themselves and not altered maternal metabolism, were the primary teratogen. A recent in vivo study has shown transfer at term but mentions that glyburide appears safe to fetus at maternal doses up to 20 mg/d and that the glyburide concentration-response relationship remains uncertain. Metformin does cross the placenta but acts as an insulin sensitizer, not insulin secretagogue and is less likely to cause severe neonatal hypoglycemia.[3,10] Because the adverse fetal consequences of maternal DM are believed to be related to fetal hyperinsulinaemia, any agent that increases fetal insulin production would not be recommended for use during pregnancy.[3] Recently, Hellmuth et al[9] followed 68 women treated with sulfonylureas during pregnancy, 50 women treated with metformin during pregnancy and a control group of 42 pregnant women with DM receiving insulin. The authors concluded that sulfonylureas seem to be well tolerated, but prospective, controlled studies are necessary before their widespread use can be recommended.

Less is known about the teratogenic risk associated with other classes of OAHAs, such as the biguanides, which include metformin and phenformin. Metformin is antihyperglycemic and not hypoglycemic. It does not cause insulin release from the pancreas and does not cause hypoglycemia, even in large doses.[9,11] The main causes of reduced glucose levels during metformin therapy appear to be due to an increase in insulin action in peripheral tissues and reduced hepatic glucose output because of inhibition of gluconeogenesis.[11] Metformin crosses the placenta,

although a partial placental barrier to metformin was observed in humans based on fetal concentrations. In 1994, Denno (cited from Balani et al[7] and Hawthorne[11]) exposed mouse embryos in culture to phenformin and metformin and examined them for embryotoxicity. Metformin produced no alterations in embryonic growth and no major malformations. In contrast, phenformin produced dose-dependent changes in the incidence of malformations, protein content, and embryo lethality. However, metformin is not without adverse effects since it produced a delay in neural tube closure in 10% of all embryos and also reduced yolk sac protein values at two different concentrations. There are several recent studies of women with polycystic ovary syndrome (PCOS) treated with metformin throughout their pregnancies.[11] Without metformin therapy, women with PCOS are frequently infertile and 44% of those who become pregnant miscarry in the first trimester

Acarbose is an oral α-glucosidase inhibitor that reduces the rise in blood glucose after meals by delaying the digestion of ingested carbohydrates. There are lack of human data regarding the use of acarbose in pregnancy, hence its use is not recommended.[4,9]

Thiazolidinediones used as an adjunct to diet and exercise to improve glycemic control in patients with type 2 DM. Currently, there are no studies on the use of thiazolidinediones during human pregnancy and thus their use for DM during pregnancy cannot be recommended.[4-5,9]

Discussion

Pros

There are various results from studies that contradict each other regarding the usage of OAHA in GDM. Balani et al[7] compared 100 women using metformin with 100 women using insulin in GDM patients. There was no difference between the metformin and insulin groups, comparing gestational hypertension, pre-eclampsia, induction of labour or rate of caesarean section. Women with GDM treated with metformin and with similar baseline risk factors for adverse pregnancy outcomes had less weight gain and improved neonatal outcomes compared with those treated with insulin.[7] A meta-analysis from 6 studies with 1388 subjects by Dhulkotia[9] shows that there are no differences in glycemic control or pregnancy outcomes when OAHA were compared with insulin. Metformin was not teratogenic and reduced the otherwise high likelihood of first-trimester miscarriage in 19 women with PCOS by ten-fold. No cases of serious neonatal hypoglycemia and a very acceptable rate of perinatal morbidity in the offspring of women with type 2 DM and GDM treated with metformin over a ten-year period. Data regarding the long-term implications of metformin use during pregnancy for offspring are limited. A cohort of 126 neonates to mothers with PCOS who took metformin through pregnancy.[8] They found no systematic differences in growth over the 18 months the infants were followed. None of the infants had experienced motor developmental delays. No infants developed neonatal hypoglycemia and the prematurity rate was comparable to community controls

Criteria for the selection of glyburide over insulin includes gestational age of 11–33 weeks, fasting glucose levels <110 mg/dL on 3-h OGTT, and no known sulfa allergy. For women who do not meet those criteria, insulin is recommended.[12] A study to determine the relative impact of maternal glycaemic control and modality of maternal anti-diabetic therapy during early pregnancy on the risk of malformations in infants and shows 2 major risk factor which are maternal glycohaemoglobin level at initial presentation for care and maternal age at onset of DM.[13] The risk of major malformations was unrelated to the mode of antidiabetic therapy during early pregnancy.[3]

Cons

Helmuth et al[10] in Denmark with 118 pregnancies that treated with OAHA shows that treatment with metformin during pregnancy was associated with increase prevalence of preeclampsia and high perinatal morbidity.

In vivo studies using mouse embryos shows that approximately 10% of all embryos exposed to metformin regardless of dose, exhibited open cranial neuropores after 24 hours of culture. A total of 20 pregnant women with type 2 DM exposed to oral hypoglycemic drugs during embryogenesis and 40 pregnant women with type 2 DM who had not been exposed. Fifty percent of the infants in the exposed group had congenital malformations, compared with only 15% of the control group.[5]

Conclusion

Insulin is still the drug of choice for GDM because it does not cross the placenta and provides very good glycemic control in patients. OAHA usage, although not yet recommended internationally, can be considered in GDM patients with uncontrolled blood sugar levels that require medical intervention but can not use insulin.

Well conducted, prospective, controlled studies regarding the feasibility of OAHAs in pregnant women with DM are still needed.

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